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a prospective cohort study (CHECK)**

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DOI

[10.1136/bjsports-2024-108222](https://doi.org/10.1136/bjsports-2024-108222)

Publication date

2024

Document Version

Final published version

Published in

British Journal of Sports Medicine

Citation (APA)

Agricola, R., Van Buuren, M. M. A., Kemp, J. L., Weinans, H., Runhaar, J., & Bierma-Zeinstra, S. M. A. (2024). Femoroacetabular impingement syndrome in middle-aged individuals is strongly associated with the development of hip osteoarthritis within 10-year follow-up: a prospective cohort study (CHECK). *British Journal of Sports Medicine*, 58(18), 1061-1067. Article 108222. <https://doi.org/10.1136/bjsports-2024-108222>

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Femoroacetabular impingement syndrome in middle-aged individuals is strongly associated with the development of hip osteoarthritis within 10-year follow-up: a prospective cohort study (CHECK)

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/bjsports-2024-108222>).

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Accepted 26 June 2024



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To cite: Agricola R, van Buuren MMA, Kemp JL, et al. *Br J Sports Med* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bjsports-2024-108222

ABSTRACT

Objective The objective is to determine the association and absolute risk of femoroacetabular impingement syndrome (FAIS) for the development of radiographic hip osteoarthritis (RHOA).

Methods This is a nationwide, multicentre prospective cohort study (Cohort Hip and Cohort Knee) with 1002 individuals aged between 45 and 65 years. Hips without definitive RHOA (Kellgren-Lawrence (KL) grade \leq 1) at baseline and with anteroposterior pelvic radiographs at baseline and 10-year follow-up available (n=1386 hips) were included. FAIS was defined by the baseline presence of a painful hip, limited internal hip rotation \leq 25° and cam morphology defined by an alpha angle $>$ 60°. The outcomes were incident RHOA (KL grade \geq 2 or total hip replacement (THR)) and incident end-stage RHOA (KL \geq 3 or THR) within 10 years.

Results Of the 1386 included hips (80% women; mean age 55.7 \pm 5.2 years), 21 hips fulfilled criteria for FAIS and 563 hips did not fulfil any of the FAIS criteria (reference group; no symptoms, no signs, no cam morphology). Within 10-year follow-up, 221 hips (38%) developed incident RHOA and 15 hips (3%) developed end-stage RHOA (including 9 hips with THR). Adjusted for sex, age and body mass index, FAIS with cam morphology resulted in an OR of 6.85 (95% CI 2.10 to 22.35) for incident RHOA and 47.82 (95% CI 12.51 to 182.76) for incident end-stage RHOA, compared with hips not having any FAIS criteria. The absolute risk of FAIS was 81% for incident RHOA and 33% for incident end-stage RHOA.

Conclusion FAIS was strongly associated with the development of RHOA within 10 years. Although the baseline prevalence of FAIS was low, the high absolute risk of FAIS for RHOA warrants further studies to determine preventive strategies.

INTRODUCTION

Osteoarthritis (OA) is a common and disabling disease with a large socioeconomic impact on individuals and society.^{1–3} Hip OA is more prevalent among athletes who practised high-impact sports at an elite level, although the underlying mechanism is unknown, making preventive measures challenging.⁴ A potential risk factor that might account for this effect is cam morphology, which is both highly prevalent in athletes and associated with the development of radiographic hip OA (RHOA) in

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Prospective cohort studies have shown an association between the radiographic presence of cam morphology and development of hip osteoarthritis (OA), although absolute risks were generally low.
- ⇒ Femoroacetabular impingement syndrome (FAIS) is a clinical condition which consists of a triad including symptoms, signs and radiographic findings (cam morphology).
- ⇒ Only two small cross-sectional studies have investigated the association between FAIS and cartilage defects in young athletic populations.

WHAT THIS STUDY ADDS

- ⇒ FAIS was strongly associated with a nearly sevenfold increased odds of hip OA within 10 years.
- ⇒ The absolute risk of FAIS for development of hip OA was high (81%), with 33% developing end-stage hip OA within 10 years.
- ⇒ By using simple and accessible measures (symptoms, a clinical hip examination and an anteroposterior pelvic radiograph), it is possible to distinguish a subgroup of people presenting with first onset hip pain at high risk for developing future hip OA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ FAIS is an important risk factor for developing hip OA and warrants additional research to define preventive strategies.

several prospective cohort studies.^{5–7} On the other hand, cam morphology is also highly prevalent in the asymptomatic population and does not necessarily lead to RHOA in all individuals.⁸ The absolute risk of cam morphology for the subsequent development of RHOA has been reported to be between 6% and 25% only.⁹

The mechanism by which cam morphology might lead to OA is femoroacetabular impingement syndrome (FAIS), a motion-related clinical disorder which represents a premature contact between the proximal femur and acetabulum.^{10–12} In a 2016 consensus meeting, it was agreed on that the diagnosis of FAIS cannot be made by the radiological presence of cam morphology alone; symptoms and

Table 1 Baseline characteristics of the included and excluded participants

	Included participants, with at least one hip included (n=744)	Excluded participants, with both hips excluded (n=258)	P value
Age, years	55.7 (5.2)	56.6 (5.2)	0.01
BMI, kg/m ²	26.2 (4.0)	26.0 (4.0)	0.43
Height, cm*	169.8 (8.4)	170.1 (8.0)	0.49
Weight, kg*	75.8 (13.2)	75.2 (14.2)	0.79
Sex			
Male	146 (20%)	64 (25%)	0.08
Female	598 (80%)	194 (75%)	

Values are mean (SD) or number (percentage).

Included participants had either one or both hips included in the analysis. In

excluded participants, both hips were excluded.

Bold value represent statistical significant difference ($p < 0.05$).

*For height and weight, total n=848 persons (154 missing).

BMI, body mass index.

clinical signs consistent with FAIS should also be present. Symptoms include motion-related or position-related hip or groin pain, and clinical signs include a limited range of internal hip rotation or a painful sensation during the flexion-adduction-internal rotation (FADIR) test.^{10 13 14} This triad (symptoms, signs and radiographic findings) should all be present to diagnose FAIS.^{10 12}

The presence of FAIS might better identify people at risk for RHOA, rather than the presence of a radiographic cam morphology alone. If this holds true, it might potentially enable preventive measures, as both surgical and non-surgical treatment options for FAIS are available.^{15 16} To date, there are only two small cross-sectional studies available which investigated the association between FAIS and cartilage defects in the athletic population aged <50 years.^{17 18} To the best of our knowledge, no prospective studies on the association between FAIS and development of RHOA are available and has recently been identified as a research priority.¹⁹

The aim of this study was to investigate the association between FAIS at baseline and the development of RHOA within 10-year follow-up and to report corresponding absolute risks.

METHODS

Study design and participants

The Cohort Hip and Cohort Knee (CHECK) study is a nationwide multicentre prospective cohort study of 1002 Dutch individuals aiming to study the cause and course of complaints of OA as well as to identify markers for diagnosis and prognosis.²⁰ Participants were eligible to enter the cohort if they had pain or stiffness in hip and/or knee and were aged 45–65 years. To be eligible, they should not yet have consulted their general practitioner for these symptoms, or the first consultation was within 6 months before entry. Participants with a pathological condition that could explain the symptoms were excluded (for hip: trauma, rheumatoid arthritis, known developmental dysplasia of the hip, Perthes disease, subluxation, osteochondritis dissecans, fracture, septic arthritis, Kellgren and Lawrence (K&L) grade 4 or total hip replacement (THR), previous hip surgery and individuals having only symptoms of bursitis or tendinopathy).

Data were obtained from 11 (general and university) hospitals. General practitioners were invited to refer eligible persons to one of those centres; advertisements in local newspapers were also used. For the hip, questionnaires and clinical hip

examination were obtained annually until 10-year follow-up. Radiographs of the hip were obtained at baseline (from October 2002 to December 2005), 2-year, 5-year, 8-year and 10-year follow-up. For the current study, baseline data were used for the exposure variables and the 10-year follow-up was used to define the outcome of RHOA. At both time points, weight-bearing anteroposterior (AP) pelvic views were obtained according to a standardised protocol which has been described previously.²¹ For the first 112 participants who entered the cohort, AP hip views instead of AP pelvic views were obtained. Of the 1002 participants at baseline, only hips free of definite RHOA (K&L ≤ 1) were included for the current study. We followed the STrengthening the Reporting of OBservational studies in Epidemiology guidelines for observational studies.

Exposure assessment

The exposure was FAIS at baseline, defined as the presence of three criteria: symptoms, clinical signs and radiographic cam morphology, according to the Warwick agreement.¹⁰

Symptoms were defined as the presence of self-reported hip pain. This was a dichotomous question and the same variable that determined at baseline whether they were eligible to participate in this cohort. For sensitivity analysis, we also used another variable of the presence/absence of self-reported hip pain or stiffness which was posed by a questionnaire ('do you have pain or stiffness in your hip, groin or upper thigh?'). Participants also had to indicate whether the symptoms were present in the right hip, left hip or both hips.

Clinical signs of FAIS were defined by a limited internal hip rotation of ≤ 25°. Hip internal rotation was measured according to a standardised protocol by a goniometer in sitting position with the hip in 90° of flexion, which previously showed satisfactory reliability.²² Due to a lack of consensus on the internal hip rotation threshold value to define FAIS, we performed a sensitivity analysis using a threshold of ≤ 20°.

Cam morphology was defined by the alpha angle on the baseline radiographs. This method has been described before.²¹ In short, the shape of the proximal femur was manually outlined with a set of points using statistical shape modelling (SSM) software (ASM toolkit, Manchester University, Manchester, the UK). From this set of points, the alpha angle was automatically calculated using a custom Matlab script (V7.1.0). The alpha angle was calculated by drawing a best-fitted circle around the femoral head. Then lines were drawn from the centre of the femoral head through the axis of the femoral neck and from the centre of the femoral head through the point where the bone leaves the fitted circle. We classified the presence of cam morphology by a validated alpha angle threshold value of > 60°. As higher alpha angles increase the risk of developing hip OA, we also present results for an alpha angle threshold of > 78°, which has previously been shown to best discriminate between hips that did and did not develop hip OA.²³ We previously reported an interobserver reliability of 0.73 and intraobserver reliability ranging from 0.85 to 0.99 for the alpha angle in this cohort.²¹

Outcome assessment

The primary outcome was incident RHOA as defined by a K&L grade ≥ 2 or a THR at 10-year follow-up. The secondary outcome was incident end-stage RHOA as defined by a K&L grade ≥ 3 or a THR at 10-year follow-up. All radiographs were scored for RHOA features using the Osteoarthritis Research Society International (OARSI) atlas, and RHOA was graded according to the K&L classification (grade 0–4) by experienced

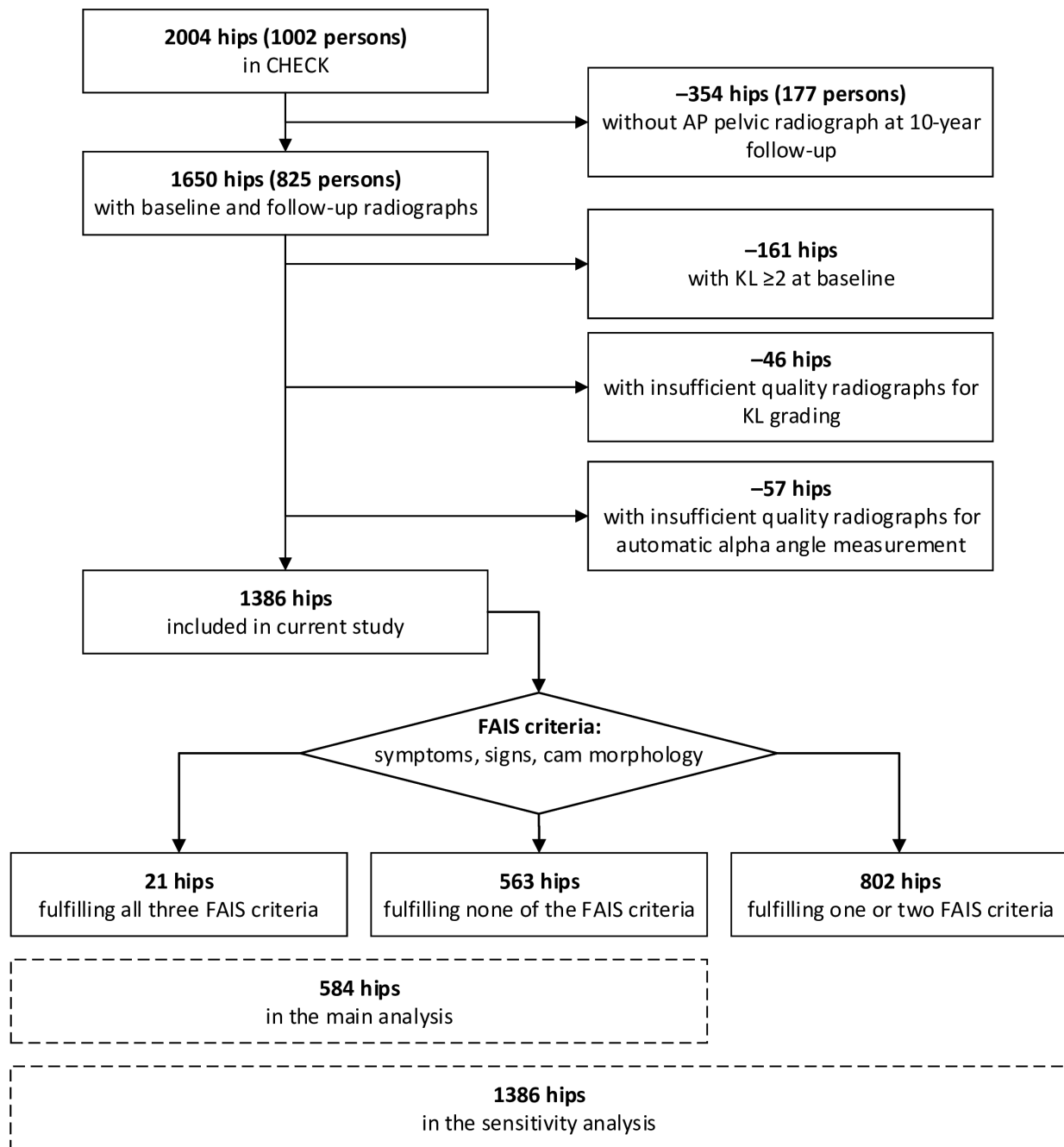


Figure 1 Flowchart of hips from cohort entry to hips included for the current study. AP, anteroposterior; CHECK, Cohort Hip and Cohort Knee; FAIS, femoroacetabular impingement syndrome; KL, Kellgren-Lawrence.

and well-trained readers.^{25–27} The radiographs of all available time points (baseline, 2-year, 5-year, 8-year and 10-year follow-up) of each participant were scored simultaneously and previously showed substantial to almost perfect interobserver reliability with average prevalence adjusted bias adjusted kappa values ranging from 0.71 to 0.91 for the different radiographic OA features.²⁸ At baseline, we only included hips with a K&L grade ≤ 1 , indicating hips without definite signs of RHOA. This way, we minimised the risk that cam morphology was misclassified due to osteoarthritic changes (eg, osteophyte formation, femoral head deformation).

Equity, diversity and inclusion

The majority of participants were women (80%) and participants were recruited from all socioeconomic levels. No particular

effort was made to include or exclude minorities. The authors are from varying career stages and disciplines, with two (33%) women.

Patient and public involvement

Two OA patients were part of the CHECK steering committee in the set-up of the study. Throughout the study period, regular patient and public meetings were held. Patients were involved in the design, interpretation of results and dissemination strategies.

Statistical analyses

The Shapiro-Wilk test was used to test for normality. Differences in baseline characteristics between included and excluded hips were evaluated by the Mann-Whitney U test for continuous

Table 2 Associations between femoroacetabular impingement syndrome and the development of incident radiographic hip osteoarthritis and incident end-stage radiographic hip osteoarthritis within 10-year follow-up

Exposure	Total n=584		Incident hip OA (KL 2–4 or THR) n=221		Incident end-stage hip OA (KL 3–4 or THR) n=15	
	N with condition	N without condition**	OR (95% CI)	aOR† (95% CI)	OR (95% CI)	aOR† (95% CI)
FAIS (hip pain, internal hip rotation≤25°, cam morphology with alpha angle >60°)	21 (3.6%)	563 (96.4%)	7.5 (2.4 to 23.4)	6.9 (2.1 to 22.4)	34.6 (10.8 to 110.8)	47.8 (12.5 to 182.8)
FAIS with large cam morphology (hip pain, internal hip rotation≤25°, large cam morphology with alpha angle>78°)	14 (2.4%)	563 (96.4%)	6.3 (2.8 to 22.4)	5.6 (1.5 to 21.5)	51.9 (14.6 to 184.9)	88.4 (17.7 to 441.4)

*The reference group for the predictor categories in this table consists of hips that did not have any of the stated conditions (eg, the reference group for FAIS are hips without cam, without hip pain, and without decreased internal rotation).
†Adjusted ORs are adjusted for age, sex and body mass index.
aOR, adjusted OR; FAIS, femoroacetabular impingement syndrome; KL, Kellgren-Lawrence grade; THR, total hip replacement.

variables and by the χ^2 test for sex. The association between baseline hips with FAIS (with all three criteria present: symptoms, signs and cam morphology) as compared with hips not having any of these criteria and the development of hip OA within 10-year follow-up were calculated using logistic regression with generalised estimating equations (GEE). The strength of association was expressed in terms of OR with 95% CIs. The use of GEE allowed for modelling the correlation between the left and the right hip in the same person. To adjust for baseline confounders, sex was entered as a factor and body mass index (BMI) and age as a covariate in the GEE model. For sensitivity purposes, we repeated this analysis using a reference group of hips that could have one or two out of three criteria of FAIS instead of a reference group with complete absence of any FAIS feature; therefore, this reference group could also contain hips with for example pain and cam morphology but an IR>25°. The absolute risk of FAIS for RHOA was calculated and expressed as percentage. If available, baseline characteristics (age, sex, BMI) of follow-up visits were used if these were missing at baseline. Missing values from questionnaire data were excluded for analysis. All statistical analyses were performed in SPSS V.25.

RESULTS

Study population

Of the 1002 individuals (2004 hips) in the CHECK cohort, 825 (1650 hips) had AP pelvic radiographs available at 10-year follow-up (82%). Of these 1650 hips, 161 hips were excluded because a K&L grade of ≥2 at baseline, 46 hips were excluded because of missing or insufficient quality baseline radiographs for reliable K&L grading and 57 hips were excluded due to insufficient quality radiographs for outlining the bone with SSM and measuring the alpha angle; leaving 1386 hips. Participants with hips excluded were slightly older and taller and more likely to be man than included participants (table 1).

Of the included 1386 hips, 21 hips fulfilled the criteria of FAIS (symptoms, signs and cam morphology), 563 hips did not fulfil any of the FAIS criteria (reference group; no symptoms, no signs, no cam morphology) and 802 hips met one or two criteria of FAIS but did not meet all three criteria (figure 1). The number of hips which meet the separate criteria of FAIS (symptomatic vs asymptomatic, signs vs no signs) can be found in online supplemental table 1. Of the 1386 hips, 16 hips had missing data for baseline BMI. In six of those, BMI was available at 1 year and in eight hips at 2-year follow-up and these values were used. Two hips (one participant) had missing data throughout the follow-up and were excluded for the adjusted analysis. For the question ‘Do you have pain or stiffness in your hip, groin or upper thigh?’, used for the sensitivity analysis, 17 hips had missing values and were excluded.

FAI syndrome and risk of RHOA

From the 584 hips at baseline for the primary analysis, 453 hips (78%) had K&L grade 0 and 131 hips (22%) grade 1. Within 10-year follow-up, 221 hips (38%) developed incident RHOA and 15 hips (3%) developed incident end-stage RHOA (including 9 hips with THR due to hip OA). None of the participants with a THR had hip surgery prior to the THR. FAIS was present in 21 hips at baseline, of which 15 also had pain on internal hip rotation. Of the 21 hips with FAIS, 9 were women and 12 were men. This resulted in an overall hip FAIS prevalence of 1.5% and a sex-specific hip prevalence of 4.6% in men and 0.8% in women. Adjusted for confounders, FAIS was associated with both incident RHOA with an OR of 6.85 (95% CI 2.1 to 22.4) and end-stage RHOA (OR=47.82, 95% CI 12.5 to 182.8). Results of unadjusted analyses and results for FAIS with cam morphology defined by an alpha angle>78° are presented in table 2. The absolute risk of FAIS was 81.0% for incident RHOA and 33.3% for incident end-stage RHOA (table 3). The

Table 3 Cross-tabulations of exposure and outcomes with corresponding absolute risks

Exposure	Incident hip OA (KL≥2 or THR)			Incident end-stage hip OA (KL≥3 or THR)		
	Present (n=221)	Absent (n=363)	Absolute risk	Present (n=15)	Absent (n=569)	Absolute risk
FAIS (hip pain, internal hip rotation≤25°, cam morphology with alpha angle>60°)						
Present (n=21)	17	4	81.0%	7	14	33.3%
Absent (n=563)	204	359		8	555	
FAIS with large cam morphology (hip pain, internal hip rotation≤25°, cam morphology with alpha angle>78°)						
Present (n=14)	11	3	78.6%	6	8	42.9%
Absent (n=563)	204	359		8	555	

FAIS, femoroacetabular impingement syndrome; KL, Kellgren-Lawrence grade; OA, osteoarthritis; THR, total hip replacement.

sensitivity analysis using the question 'do you have pain or stiffness in your hip, groin or upper thigh' from the questionnaire to define hip/groin pain instead of the self-reported hip pain variable showed similar statistically significant results (online supplemental table 2). Similar results were also found for the sensitivity analysis using an internal hip rotation threshold of $\leq 20^\circ$ instead of $\leq 25^\circ$ (online supplemental table 3). Results from the sensitivity analysis using all hips that did not fulfil all three criteria of FAIS (hip pain, decreased internal rotation and cam morphology) are presented in online supplemental table 4 and showed significant associations between FAIS and both incident RHOA and incident end-stage RHOA.

DISCUSSION

In this first prospective cohort study on the relationship between FAIS and the development of RHOA, we showed a strong relationship between FAI syndrome and development of RHOA within 10 years and corresponding high positive predictive values. Although the prevalence of FAIS was low in this cohort of people aged between 45 and 65 years, this subgroup of people at high risk for developing RHOA could be identified using simple and accessible measures (clinical hip examination and an AP pelvic radiograph) from people that present with first onset of either hip or knee complaints to the general practitioner.

Previous prospective cohort studies have only investigated the relationship between the radiographic presence of cam morphology and development of RHOA and consistently showed a positive association.^{5 6 29} The strength of association between cam morphology and development of hip OA in prospective cohort studies ranged between ORs of 2.1 (95% CI 1.6 to 2.9) and 9.7 (95% CI 4.7 to 19.8).^{21 30–33} Two small studies investigated the cross-sectional relationship between FAIS and MRI detected cartilage defects in younger (18–50 years) individuals.^{17 18} In one study, individuals with FAIS showed cartilage defects more frequently than asymptomatic controls.¹⁸ In the other study, cam morphology was associated with cartilage defects and labral tears in athletes although the presence or absence of symptoms did not influence this association, meaning that the association found was similar between those with FAIS and asymptomatic controls.¹⁷ Interestingly, in the same cohort, symptoms were associated with cartilage loss severity in men indicating that the relation between hip and groin pain, FAIS and (early) hip OA is still poorly understood.³⁴ The cartilage lesions found in these studies of people aged < 50 years might be a precursor of definite OA later in life, as found in this study of people aged > 45 years.

The high absolute risks found in this study support the necessity for increased awareness for FAIS and justify more research into possible preventive options to halt or delay the progression from FAIS towards hip OA. Previous epidemiological studies investigating only the radiographic presence of cam morphology reported absolute risks for hip OA between 6% and 25%.⁹ This suggests that although the radiographic presence of cam morphology is strongly associated with hip OA, the majority of hips with cam morphology will still not develop OA. In contrast, the absolute risk for FAIS ranged between 33% and 81% dependent on the size of cam morphology and definition of OA used. Adding symptoms and limited internal rotation to the presence of cam morphology enhances the likelihood of the prediction of hip OA. Hips with cam morphology with a larger range of internal hip rotation might not cause impingement and could therefore be less likely to result in hip OA.

There are opportunities for both primary and secondary prevention. Primary prevention would include some sort of activity modification during growth, as cam morphology develops during adolescence when the proximal femoral growth plate is still open.³⁵ The formation of cam morphology is triggered by the loads applied to a growing hip, resulting from athletic activities, as cam morphology is rare in non-athletes.^{36 37} Although the exact mechanism in terms of loading pattern, frequency and duration of loading in cam morphology development is still unknown, and such prevention programmes might be challenging to implement, there is a theoretical opportunity for primary prevention. Challenges that come with primary prevention are the conflict between load reduction during a given time-frame and the recommendations for adolescents to engage in sports, particularly at an age where skill development and talent identification is important.³⁸ Secondary prevention might be more feasible to implement and can include strategies to prevent the cam morphology from causing intra-articular damage. One could think that activity modification to prevent impingement between cam morphology and the acetabulum,³⁹ strength training,⁴⁰ improving balance,⁴¹ and functional movement,⁴² education about the importance of exercise and physical activity,³⁹ and other forms of physio-therapist-led rehabilitation⁴³ that target impairments could all be useful. Another secondary preventive option could be to surgically remove cam morphology. Although recent randomised controlled trials show a clinical benefit of both approaches in the short term, there is no long-term evidence available on secondary prevention of hip OA.^{15 16}

There are several strengths and weaknesses in this study that need to be acknowledged. Strengths are the prospective design and large sample size. Despite the large sample size, only 21 hips fulfilled the criteria of FAIS. One of the reasons is the higher proportion of women in this cohort, who have a lower prevalence of cam morphology and FAIS than men. Given the low prevalence of FAIS, the strength of association needs to be interpreted with caution, as the CIs around the ORs are wide. Larger prospective studies are needed to refine the strength of association. In the definition of FAIS, we used limited internal hip rotation as the clinical sign, which has recently been described to be best for ruling in FAIS, although the quality of evidence of available studies was low.¹⁴ The Flexion Adduction Internal Rotation (FADDIR) test has also been described as a clinical sign of FAIS, and its use has rather been suggested to rule out FAIS,^{13 14} but the FADIR test was not available in this cohort. We only used AP pelvic radiographs to quantify cam morphology, which might have led to an underestimation of cam morphology prevalence. We only examined FAIS with cam morphology because FAI with pincer morphology follows another mechanism, and the relation between pincer morphology with OA has previously shown to be inconsistent.^{29 44} Therefore, we cannot draw any conclusions on FAIS with pincer morphology, which will need further study. Finally, the control group of non-FAIS hips at baseline also included people with first onset of knee pain and might not represent a control group completely free of pain.

CONCLUSION

FAIS was strongly associated with development of hip OA within 10 years. Although the prevalence of FAIS was low, the majority of people with FAIS developed OA within 10 years. The high

absolute risk of FAIS for developing hip OA warrants further studies on preventive strategies.

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Acknowledgements The authors would like to thank all the participants of the CHECK cohort. CHECK cohort study is initiated by the Dutch Arthritis Association and performed within Erasmus Medical Center Rotterdam, Kennemer Gasthuis Haarlem, Leiden University Medical Center, Maastricht University Medical Center, Martini Hospital Groningen/Allied Health Care Center for Rheumatism and Rehabilitation Groningen, Medical Spectrum Twente Enschede/Ziekenhuisgroep Twente Almelo, Reade, formerly Jan van Breemen Institute/VU Medical Center Amsterdam, St Maartens kliniek Nijmegen, University Medical Center Utrecht and Wilhelmina Hospital Assen.

Contributors All authors substantially contributed to the conception or design of the work; the acquisition, analysis or interpretation of data for the work and drafting the work (RA) or revising it critically (MMAvB, JLK, HW, JR, SMAB-Z) for important intellectual content and final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RA is the guarantor.

Funding The CHECK study was funded by the Dutch Arthritis Society. The current study was part of projects funded by the Dutch Arthritis Society (21-1-205) and ZonMw (VENI 09150161910071).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by IRB of Utrecht University Medical Centre. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data are available on reasonable request. The data underlying this article cannot be shared publicly due to legal reasons as well as the privacy of individuals that participated in the study.

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